National German Guideline (S2k): Guideline for the Diagnosis and Treatment of Endometriosis

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Leitlinie für die Diagnostik und Therapie der Endometriose

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Key words
- endometriosis
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- Endometriose
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Abstract

In this guideline, recommendations and standards for optimum diagnosis and treatment of endometriosis are presented. They are based on the analysis of the available scientific evidence as published in prospective randomized and retrospective studies as well as in systematic reviews. The guideline working group consisted of experts from Austria, Germany, Switzerland, and the Czech Republic.

Zusammenfassung

Mit dieser Leitlinie werden Empfehlungen und Standards für eine optimale Diagnostik und Therapie der Endometriose vorgestellt. Sie basieren auf einer Analyse prospektiv-randomisierter und retrospektiver Studien sowie systematischer Übersichten. Die Arbeitsgruppe bestand aus Experten aus Deutschland, Österreich, der Schweiz und Tschechien.

The Guideline is Supported by the Following Professional Associations and Organizations:

- German Society for Obstetrics and Gynecology (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V., DGGG)
  - Gynecological Endoscopy Study Group (Arbeitsgemeinschaft für Gynäkologische Endoskopie, AGE)
  - Gynecological Oncology Study Group (Arbeitsgemeinschaft für Gynäkologische Onkologie e.V., AGO)
  - German Society for Gynecological Endocrinology and Reproductive Medicine (Deutsche Gesellschaft für Gynäkologische Endokrinologie und Fortpflanzungsmedizin e.V.)
- German Society for Psychosomatic Obstetrics and Gynecology (Deutsche Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe, DGPFG)
- German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e.V., DGAV)
- German Society for Urology (Deutsche Gesellschaft für Urologie e.V.)
- Austrian Society for Obstetrics and Gynecology (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe e.V., ÖGGG)
- Swiss Society for Obstetrics and Gynecology (Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe, SGGG)
- Czech Society for Obstetrics and Gynecology
- Endometriosis Research Foundation (Stiftung Endometriose-Forschung, SEF)
- European Endometriosis League (EEL)
- Endometriosis Association of Germany (Endometriose-Vereinigung Deutschland e.V.)
- Endometriosis Association of Austria (Endometriose-Vereinigung Austria)

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1 Background

In this guideline, a standard is recommended for the diagnosis and treatment of endometriosis on the basis of the previously published scientific knowledge and of the experience of the authors. Doctors providing care for patients with endometriosis represent the target group for this guideline.
The recommendations are based on an analysis of the scientific literature (PubMed, MEDLINE search, Cochrane Library), although only a limited number of prospective, randomized studies are available on the diagnosis and treatment of endometriosis.
The recommendations and publications of the following professional associations were also taken into consideration:

- Endometriosis Research Foundation (http://www.endometriose-sef.de)
- The Royal College of Obstetricians and Gynaecologists Clinical Green-Top Guidelines for the Investigation and Management of Endometriosis (http://www.rcog.org.uk/)
- ESHRE Guideline for the Diagnosis and Treatment of Endometriosis (http://www.eshre.eu)
- The American College of Obstetrics and Gynecology Committee on Practice Bulletins (http://www.acog.org/)
- awmf.de [86]

2 Introduction

2.1 Definition and epidemiology

Core statements:

a. Endometriosis is defined as the presence of endometrium-like groups of cells outside the uterine cavity.
b. The cardinal symptom is pelvic pain, and infertility is common.

Endometriosis is one of the most common gynecological diseases. It occurs predominantly after sexual maturity has been reached and is considered to be estrogen-dependent. In one study, adolescents in the 10- to 15-year-old age group represented 0.05 % and in the 15- to 20-year-old age group 1.93 % of all women with endometriosis. Postmenopausal women accounted for 2.55 % of the cases [78]. Endometriosis is a cause of significant morbidity [5, 68, 172].
Reliable information on frequency is lacking, and there are significant fluctuations in the prevalence rates quoted in the literature. It is estimated that approx. 40 000 new cases occur in Germany each year. Around 20 000 women are admitted for hospital treatment for endometriosis each year in Germany [78]. The economic impact is considerable in terms of medical cost and reduced work productivity. Despite this, the disease is under-represented in clinical and basic scientific research [168].
The dilemma of endometriosis is caused partly by the long interval between the appearance of the first symptoms and the correct diagnosis – 10 years on average in Austria and Germany [91] – and partly by the repeated operations in chronic forms of the disease.
Although endometriosis is a histopathologically benign disease, it can spread to other organs as a result of infiltrative growth and require extensive surgery [189].

2.2 Etiology, pathology and staging

Core statement:

The etiology and pathogenesis of endometriosis are still not fully understood. There is, therefore, no known causal treatment at present.

Recommendation:

All known staging systems have their limitations. For the purpose of international comparability, the rASRM staging system should be used, with the addition of the ENZIAN classification in deep infiltrating endometriosis.

Various theories on the etiology and pathology of endometriosis have been presented in the literature: implantation theory [164, 165], celomic metaplasia theory [126], archimetra or “tissue injury and repair” concept [113, 114].
The most widely used classification is that of the American Society for Reproductive Medicine (the “rASRM score”, [11]). This rASRM score shows only a weak correlation with the cardinal symptoms of pain and infertility [72, 194]. The description of retroperitoneal and deep infiltrating growth forms is also inadequate with this system. The Endometriosis Research Foundation has attempted to overcome this shortcoming by creating an appropriate classification – the ENZIAN classification [77, 79, 80, 157, 186]. Like the rASRM score, the ENZIAN classification is also morphologically descriptive. At present, no data exist showing whether the ENZIAN classification correlates with symptoms such as pain and infertility. The traditional division into external and internal genital endometriosis and extragenital endometriosis [9] has proven useful in routine clinical practice; it takes into account the concept of a single disease entity.
In decreasing order of frequency, the following are involved: pelvic peritoneum, ovaries, uterosacral ligaments, rectovaginal septum/vaginal fornix, and extragenital sites (e.g., rectosigmoid colon and urinary bladder).
The incidence of involvement of the uterus (adenomyosis) and tubes is not entirely clear. The diaphragmatic peritoneum [137, 155], the vermiform appendix [71] and the umbilicus [197] are rare but typical extragenital sites. Endometriosis also occurs in surgical scars following hysterectomy, cesarean section, episiotomy, and perineal lacerations [19, 62, 144, 167]. It is debated that this may be caused by the mechanical transfer of endometrial particles. Manifestations in the spleen, lungs, kidneys, brain or skeleton are rare.

Patient information – Causes of endometriosis

The causes of the development of endometriosis have not yet been scientifically proven. No causal treatment options are, therefore, available at present which might enable endometriosis to be eliminated completely or cured.
There is also no treatment available that prevents endometriosis from developing in the first place.

Endometriosis and malignancy

Core statements:

a. In very rare cases, malignancy may arise from endometriosis – usually ovarian cancer.

b. An association with the occurrence of other, non-gynecological malignancies can also be found in the literature. The clinical significance of this observation is unclear.

Risk of malignant diseases in women with endometriosis

Even though there is no statistically detectable increase in the risk of cancer for women with endometriosis in general [122, 181], an association has been described between the existence of endometriosis and certain malignancies such as endocrine tumors, ovarian cancer, renal cell carcinoma, brain tumors, malignant melanoma, non-Hodgkin lymphomas and breast cancer [28, 82, 122, 136, 139, 148, 198]. The standardized incidence ratio (SIR) is stated as, for example, 1.38 for endocrine tumors, 1.37 for ovarian cancer and 1.08 for breast cancer [122]. The SIR might be even higher in women with primary infertility, endometriosis and one of the aforementioned malignancies [27]. The validity of these data and their clinical significance are unclear.

Endometriosis-associated malignancies Malignant tumors may arise from endometriosis. Ovarian cancer accounts for around 80% and extragonadal tumors for 20% of these cases [187, 199], with the positive correlation persisting even if it was many years previously that the woman had the endometriosis [148]. Endometriosis is considered to be a risk factor that can accelerate the development of ovarian cancer by 5 years [12]. According to one study, the overall risk is approx. 2.5% [190]. Histologically, the tumors are mainly of the endometrioid (OR 3.05) or clear cell (OR 2.04) type, although a correlation has been found recently between endometriosis and well differentiated (G1) serous carcinomas (OR 2.11) [148]. The association between poorly differentiated (high-grade) serous and mucinous ovarian carcinomas or borderline ovarian tumors is not statistically significant [148]. Other histologic entities occur (endometrial stromal sarcoma, mixed tumors, etc.) [200]. Furthermore, an ovarian endometrioma diameter of ≥ 9 cm, a postmenopausal situation [106] and a hyperestrogenic state [206] are reported to be independent risk factors (single center data). In the Swedish Hospital Discharge Registry of 2004, the presence of endometrial cysts in women between 10 and 29 years of age was defined as an additional risk factor for the subsequent development of ovarian cancer [25]. Ovulation inhibitors, births, tubal sterilization or hysterectomy might reduce the risk, on the other hand [128]. Extragonadal endometriosis-associated carcinomas have virtually been described in almost all tissues in which endometriosis occurs [121].

Summary On the basis of the described incidence rates and risk factors, the possibility of endometriosis-associated malignant disease should be included in considerations relating to differential diagnosis, and patients should be informed about this accordingly. At the same time, it is important to exercise prudence and to keep a sense of proportion when confronting endometriosis patients with these statements.

Patient information – Endometriosis and malignancy

Even if women with endometriosis are not generally at increased risk of malignant disease, some malignant diseases may occur more frequently than in women who do not have endometriosis.

The work-up for and treatment of endometriosis should, therefore, take this fact and the individual situation of the woman concerned into account.

Specific additional investigations may thus be required in individual cases.

3 Diagnosis and Treatment of Endometriosis

Core statements:

a. Indications for endoscopic diagnosis and treatment in endometriosis are as follows:
- Pain
- Organ destruction, and/or
- Infertility

b. Surgical removal of the lesions is considered the "gold standard" for symptom control [1, 50, 67].

Recommendation:

In general, the diagnosis of endometriosis is to be established histologically. Hence, laparoscopy is essential for the diagnostic work-up [202].

3.1 General remarks

Some of the women affected are asymptomatic. Furthermore, the disease stage does not correlate with the severity of the symptoms [70, 161]. The determination of CA-125 levels is not helpful either for diagnosis or follow-up and is not recommended (see section 3.3.1, [131]). In some cases, it is difficult to prove whether a causal relationship actually exists between endometriosis and certain symptoms. Asymptomatic endometriosis in a patient who does not wish to become pregnant is not generally an indication for surgical or medical intervention. There are exceptions to this, e.g., endometriosis-induced ureteral stenosis with hydronephrosis (absolute indication). Almost all women with *symptomatic* endometriosis suffer from dysmenorrhea. If this cardinal symptom is absent, other causes of pelvic pain must be considered in the differential diagnosis [173, 174].

For the sake of clarity, the different forms of endometriosis are discussed separately. Nevertheless, they are often combined [188].

Patient information – General notes on diagnosis and treatment

In the presence of suspected endometriosis, a histologic assessment should be performed. As a general rule, laparoscopy is necessary for this.

Persistent pain, desire to conceive and/or functional impairment of an affected organ (e.g. ovaries, bowel or ureter) are reasons for the surgical and/or pharmacological treatment of endometriosis. Conversely, it follows that a woman who has endometriosis but does not have any symptoms, does not wish to conceive and does not exhibit any organ damage, does not need to be treated, although it is always important to consider the patient's individual situation.

3.2 Peritoneal endometriosis

Core statements:

a. Peritoneal endometriosis is diagnosed laparoscopically.

b. The treatment of choice is laparoscopic removal of the implants.

Recommendation:

Following medical suppression of the ovarian function, endometriotic implants may undergo regression. To reduce endometriosis-associated symptoms, progestins, oral contraceptives or GnRH analogs can be used in order to induce therapeutic amenorrhea.

3.2.1 Morphology and symptoms

In peritoneal endometriosis, a distinction is made between red, white and black lesions [11] and/or between pigmented and non-pigmented (atypical) lesions [95,138]. The red and non-pigmented lesions are seen as early manifestations of endometriosis. They are considered to be particularly active. In terms of response to hormone therapy, peritoneal endometriosis appears to differ from ovarian and deep infiltrating endometriosis [138]. It is not known, however, whether the different forms of peritoneal endometriosis behave differently in relation to pain, fertility and course of the disease [75]. Patients with pronounced symptoms prior to surgery are at higher risk of recurrence than patients who do not feel much pain [156]. The lifetime risk of endometriosis recurrence depends on the age at initial diagnosis and is 1.75-fold higher for 20- to 29-year-old than for 30- to 39-year-old patients [171]. Early diagnosis of endometriosis, including in adolescent girls, might be of significance in terms of the subsequent course of the disease and the maintenance of fertility [4,204].

3.2.2 Diagnosis

Following a detailed past medical history-taking and vaginal/rectal examination, the key measure for diagnosing peritoneal endometriosis is laparoscopy with histologic confirmation [67]. Transvaginal ultrasonography or MRI are equally irrelevant to the detection of peritoneal implants, although the former serves to rule out ovarian endometriosis [132], and the latter may provide additional information where deep infiltrating endometriosis is present at the same time [105].

3.2.3 Treatment

Surgical treatment Laparoscopic removal of the lesions is the primary therapeutic objective. This has been shown to reduce the pain [93]. Whether the methods available (coagulation, vaporization, excision) are equivalent is unclear [81]. Additional LUNA (laparoscopic uterine nerve ablation) does not lead to any improvement in outcome in patients with minimal to moderate endometriosis who have pain [196]. It has not been proven whether postoperative pharmacological suppression of ovarian function is successful in improving the effect of surgery or maintaining it for longer [64].

One option for reducing persistent pain after surgery is the insertion of a levonorgestrel-releasing IUD [2].

Primary medical treatment Suppression of ovarian function produces regressive changes in endometriotic implants. A reduction in endometriosis-associated symptoms can be achieved equally with progestins, oral contraceptives (continuous) or GnRH analogs [29,73,211], while GnRH analogs were more effective for dysmenorrhea and dyspareunia in some studies. Differences exist in terms of the adverse effect profiles and costs, however [30,47,84,193]. In two current, prospective and randomized studies, continuous oral administration of a progestin (dienogest) has been shown to have the same efficacy as a GnRH analog in endometriosis-associated pain, while dienogest offered advantages for the patient in terms of clinical tolerability [74,180]. Long-term data show a sustained clinical effect continuing beyond the period of administration [151].

When administered over a more prolonged period of time, GnRH analogs should be administered concomitantly with appropriate protective add-back medication because of the potential effects of estrogen deficiency. The duration of treatment with GnRH analogs is 6 months in patients with pain. Although a 3-month treatment period is just as effective, it is associated with a shorter recurrence-free interval [83]. No data are available on the benefit of extended GnRH-a therapy. According to the findings of one prospective study, treatment with dienogest as maintenance therapy after GnRH-a was effective in maintaining the GnRH-a-induced effect for at least 12 months [103]. Although non-steroidal and other anti-inflammatory drugs are used frequently in routine clinical practice, there is no evidence at present that they have a positive influence on the specific symptoms associated with endometriosis [10].

3.3 Ovarian endometriomas

Core statement:

The diagnosis of ovarian endometriomas is primarily made by transvaginal ultrasound.

Recommendations:

a. For primary treatment of ovarian endometriomas, the cyst wall should be removed surgically. Fenestration alone is insufficient.

b. Hormonal drug treatment alone is neither effective in eliminating an ovarian endometrioma and thus to replace its surgical removal, nor in compensating for incomplete surgical removal. Therefore, it is not recommended.

3.3.1 Diagnosis

In 20–50% of all women with endometriosis, the ovaries are affected [89]. The preoperative work-up is based on the clinical examination and transvaginal ultrasound, with ovarian endometrioma often exhibiting a typical echo texture [88]. However, sonographically complex ovarian masses with a heterogeneous appearance are also found, which makes it difficult to distinguish between functional cysts on the one hand and dermoid cysts, cystomas or ovarian cancer on the other in individual cases [109] (**Table 1**). In the case of planned laparoscopic procedures in the presence of unclear ovarian findings, reference is made to the relevant S1 Guideline of the German Society for Obstetrics and Gynecology (Guideline: laparoscopic surgery for ovarian tumors, AWMF no. 015-003). Any unclear ovarian mass should be evaluated histologically.

If there is pain, additional deep infiltrating endometriosis is probably present [40] which must be taken into consideration during the clinical examination.

Table 1 Ultrasound appearance of ovarian endometrioma in premenopausal women (modified according to [88, 191]).

Appearance:	heterogeneous
Size:	up to 15 cm
Borders:	smooth
Wall thickness:	increased
Echogenicity:	not anechogenic (hypo- to hyperechogenic)
Internal echoes:	fine, uniformly distributed
Further features:	one or more compartments
	uni- or bilateral
	The same characteristics are associated with a higher risk of malignancy in postmenopausal women.

Determination of tumor markers The CA-125 value is often assessed in the differential diagnostic work-up of complex ovarian masses. As the CA-125 value is commonly elevated in endometriosis patients, however, it is of no relevance in terms of the differential diagnosis (Guideline: laparoscopic surgery for ovarian tumors, AWMF no. 015-003). It is not sufficiently specific. Therefore, its determination for the evaluation of suspected endometriosis is not recommended in the clinical routine. In the course of the disease (e.g., in a suspected recurrence), the clinical situation is the decisive factor rather than the CA-125 level. The same applies at present to serum levels of human epididymis secretory protein 4 (HE4) [112, 207].

3.3.2 Treatment

The most effective treatment for ovarian endometriomas is their surgical removal. The method of choice for this is surgical laparoscopy [32]. According to a meta-analysis, ovary-sparing removal (extraction) of the cyst wall is superior overall to thermal destruction using a high-frequency current, laser vaporization or argon plasma coagulation in terms of pain symptoms and recurrence and pregnancy rates [76]. Whether this recommendation should apply only to endometriomas with a diameter of > 4 cm is a moot point [85, 100]. The problem of the potential loss of oocytes following the excision of recurrent endometriomas in infertility patients resulting in the procedure not being performed prior to assisted reproduction (but therefore also in no histologic confirmation being obtained) in the case of smaller endometriomas, will be examined later in detail in section 4.3. The experience of the surgeon may have an influence on this oocyte loss [205].

The opening and drainage of the cyst capsule of the endometrioma cannot be recommended as a surgical procedure alone because 80 % of patients receiving this treatment suffer a recurrence within six months [7, 162]. This high recurrence rate cannot be reduced by subsequent treatment with GnRH analogs [192].

Medical (hormonal) treatment for ovarian endometriomas alone is not sufficient and is not recommended. Pre-operative administration of GnRH analogs may lead to a decrease in the size of the endometrioma. Whether this results in surgical benefits or a reduction in recurrence rates is the subject of controversy in the literature [53, 134]. Postoperative GnRH analogs do not compensate for incomplete surgery [33]. While some working groups have been able to show that postoperative administration of a hormonal contraceptive resulted in a reduction in the recurrence rate [135, 169, 182], two other prospective, randomized, placebo-controlled trials showed low recurrence rates irrespective of the treatment arm [8, 170].

Patient information – Ovarian endometriosis

An endometriotic ovarian cyst should be removed completely by means of laparoscopy.

Hormonal treatment alone is not sufficient.

3.4 Deep infiltrating endometriosis

Core statements:

a. Deep infiltrating endometriosis (DIE) is defined as the involvement of the rectovaginal septum, the vaginal fornix, the retroperitoneum (pelvic side wall, parametrium), the bowel, ureter, and urinary bladder.

b. The primary diagnosis is made clinically with rectovaginal palpation, inspection with divided specula, transvaginal ultrasound and transabdominal ultrasound of the kidneys being mandatory.

Recommendations:

a. For treatment, complete resection should be performed. Nonetheless, compromises must be made as preservation of fertility often is imperative.
The extent of the resection should be decided in close agreement with the patient against the background of benign disease and possible relevant complications.

b. The treatment of DIE should take place in dedicated specialist centers on the basis of an interdisciplinary approach.

c. In the case of conservatively managed patients and before and after surgery, kidney ultrasound is mandatory in order to avoid overlooking clinically silent hydronephrosis. Hydronephrosis associated with DIE is an absolute indication of appropriate diagnosis and treatment.

3.4.1 Symptoms

DIE refers to the forms which manifest in the rectovaginal septum, in the vaginal fornix, in the retroperitoneum (pelvic side walls, parametrium) and in the bowel, ureter and urinary bladder. In the case of ureteral endometriosis, a distinction is made between the intrinsic (infiltration of the ureter itself; rare) and extrinsic (external compression) subtypes. The way in which the aforementioned structures are involved may be very complex [189].

The symptoms depend on the site. In the case of bowel involvement, various intestinal symptoms occur, including dyschezia, feeling of pressure, flatulence, tenesmus, blood and mucus in the stool, diarrhea and constipation, and altered bowel habits. The absence of symptoms does not rule out bowel involvement. Endometriosis of the bladder can cause voiding difficulties and hematuria. Ureteral endometriosis can lead to hydronephrosis. Endometriosis-induced back-up of urine develops slowly and is, therefore, usually clinically silent [177]. Dyspareunia is typically caused by alteration of the pelvic plexus [154]. Although most patients with DIE complain of a variety of bowel symptoms, it has not been possible so far to reproduce any sensitive anorectal dysfunction by means of manometry in studies on this subject [118].

Rectovaginal septum involvement is most common, followed by involvement of the rectum, the sigmoid colon, the cecum and the vermiform appendix, the bladder and ureters and, much more rarely, the ileum while multiple sites involvement is possible.

3.4.2 Diagnosis

A clinical diagnosis of suspected disease is made initially on the basis of the patient's history, which is often indicative, and on vaginal and rectal palpation, followed by an investigation-based diagnosis by means of transvaginal ultrasound. Various investigations have been found to be useful in connection with the subsequent work-up (**Tables 2** and **3**):

Table 2 Clinical investigations for the work-up of deep infiltrating endometriosis.

Investigation	Evidence provided
Inspection (double-bladed speculum)	Visible endometriosis in the posterior fornix
Palpation (always including rectal)	Uterus often retroverted; dense, nodular, tender infiltration of the rectovaginal septum (retrocervical)
Transvaginal ultrasound	Changes in the uterus in the presence of concurrent adenomyosis and information about possible ovarian endometriomas, good visualization of deep rectal involvement
Renal ultrasound	Be alert to back-up of urine (parametrial, pelvic wall and ureteral endometriosis)

Table 3 Optional investigations for the evaluation of deep infiltrating endometriosis.

Investigation	Evidence provided
Proctosigmoidoscopy	External impression, mucosal involvement (rare), differential diagnosis of primary bowel disease
Magnetic resonance imaging	Involvement of the bowel wall, the bladder; adenomyosis?
Transrectal endoscopic ultrasound	Involvement of the bowel wall?
Contrast enema	Bowel involvement in higher sections
Intravenous pyelogram or computed tomography	Ureteral stenosis, hydronephrosis
Cystoscopy	Bladder involvement

Proctosigmoidoscopy is used very frequently in the presence of suspected rectosigmoid involvement. However, infiltration of the mucosa is extremely rare. In the presence of extensive disease, an external impression is rather to be expected – around 26% of patients with rectal endometriosis exhibit stenosis [161], so a negative proctoscopic mucosal finding is the rule, and by no means excludes involvement of the muscularis. The importance of proctoscopy thus lies in the evaluation of other causes of rectal bleeding as part of the differential diagnosis. MRI exhibits a high sensitivity for the diagnosis of DIE and provides useful information [18]. Transrectal endoscopic ultrasound provides a reliable and simple means of predicting the presence of deep rectal infiltration [18]. Transvaginal ultrasound also provides a straightforward means of DIE visualization, including the diagnosis of deep rectal involvement with a high level of sensitivity and specificity combined with minimal patient discomfort [87,90]. In a comparative study, the aforementioned methods were found to be equivalent overall in terms of diagnostic effectiveness, although MRI had the highest sensitivity in some cases [18]; in another study, transvaginal ultrasonography was favored [3]. Regardless of the pre-operative diagnosis, the extent of the resection is often not decided until during the operation (e.g. multiple intestinal foci: rectum, sigmoid colon, cecum).

3.4.3 Treatment

The treatment of choice for symptomatic deep infiltrating endometriosis is resection, leaving a free margin on all sides [42,61,98,125,127,153]. In many studies, a positive effect on pain, overall quality of life and fertility has been demonstrated [17]. Various methods are available for this: vaginal resection, laparoscopy, laparoscopically assisted vaginal surgery, laparotomy. In the presence of infiltration-related manifestations of endometriosis (rectosigmoid colon, bladder, ureter), the pre-operative counseling for and planning and performance of the intervention should be carried out on the basis of interdisciplinary consensus (including Visceral Surgery and/or Urology, depending on the situation). If hydronephrosis is present (i.e., an absolute indication of treatment), it is vital to refer the patient to a urologist who will carry out an assessment of renal function and decide whether, how, and to what extent treatment should be carried out [117]. If there is a desire to conceive, the need to preserve the uterus and ovaries often results in incomplete resection of the endometriosis.

The benefits of the resection are to be confronted with the morbidity associated with surgery [31,36,45,154] as well as the recurrence rate of endometriosis. Recurrences after bowel resection for DIE occur in about 14% of cases (5–25%, see [49,124]). Complications, some of which can be severe (anastomotic leaks), must be anticipated during surgery and in the immediate postoperative period in approx. 5–14% of cases. This applies especially to segmental rectal resection (associated with an incidence of up to 24%, see [108,127,147,150,160]), which is why some research teams warn against segmental rectal resection for benign endometriotic disease and recommend the mucosa-sparing "shaving" technique or full-thickness resection of the wall without in-continuity resection [54,69]. The long-term consequences – some of which being irreversible – must always be weighed against the desired positive effect of the operation. Besides fistula and rectal dysfunction [13], bladder atony – sometimes associated with the need for permanent self-catheterization by the patient – is of particular clinical relevance [15,160]. This is caused by surgical alteration of the hypogastric plexus (splanchnic nerves) which is unavoidable in some cases. The risk of postoperative bladder atony with self-catheterization was stated as 29% in one study; the risk was associated with simultaneous partial colpectomy [210]. Whether nerve-sparing surgical techniques can prevent such urological complications is under investigation [37,97]. A particular situation also arises when complex colorectal and urological procedures are performed in one session – in these cases, it is important to consider whether it would not be better to adopt a two-step approach [159].

Owing to the complexity of the procedures, surgical treatment of DIE should be carried out in centers with relevant experience [56]. Asymptomatic findings should always be monitored with the inclusion of renal ultrasound, and do not necessarily require surgery in the absence of progression. Spontaneous bowel perforation and ileus are extremely rare [51]. Because of the risk of these occurring, however (e.g., including during pregnancy with considerable maternal and fetal consequences in some cases), the pros and cons of a deliberate decision not to operate should also be discussed in detail. This gives rise to the dilemma that both surgery for deep rectovaginal endometriosis and leaving it in situ may possibly result in a higher risk of spontaneous perforation/vulnerability during pregnancy and delivery (posterior vaginal fornix rupture), which is attributed to decidualization during pregnancy [24,41,152]. Against this background, the primary method of delivery (spontaneous delivery versus cesarean section) is a subject which should definitely be broached with the patient and considered carefully (expert opinion, Weissensee meeting of the Endometriosis Research Foundation, 2013). Conclusion: Possible surgical and non-surgical alternatives for DIE must always be explained in both directions (documentation).

The benefit of pre- or postoperative GnRH analog therapy for deep infiltrating endometriosis is not proven [33,64], and, therefore, cannot generally be recommended. Medical hormonal therapy will be given, however, if the patient wishes to avoid surgery or if there are postoperative symptoms. An effect can only be expected during therapy, and long-term treatment is therefore necessary. Progestin monotherapy, a monophasic continuous oral contraceptive or GnRH analogs (with add-back therapy) for the induction of therapeutic amenorrhea are options. Another possible alternative to surgery is the insertion of a levonorgestrel-releasing IUD under which pain relief and a reduction in rectovaginal endometriosis size have been observed [59].

Estrogen and progestogen replacement therapy in endometriosis Premenopausal patients following hysterectomy for endometriosis receive combined estrogen and progestin replacement therapy if indicated. In postmenopausal women, estrogen and progestogen combinations or tibolone are also recommended following hysterectomy in view of the fact that there is a risk of recurrence and malignancy (see section entitled "Endometriosis-associated malignancies") [129,175]. The problem of the risk of breast cancer must nevertheless be weighed against this and discussed with the patient so that an individual decision can be made (AWMF-S3 Guideline: Hormone replacement therapy in peri- and postmenopausal women, AWMF Registry no. 015-062, 2009).

Patient information – Deep infiltrating endometriosis

Where endometriosis involves the vagina, bowel, bladder and ureters, complete surgical removal of the lesions is the best treatment at present. Extensive surgery is often needed for this, which requires good cooperation between gynecologists, surgeons and urologists and should be performed in a dedicated specialist unit.

Before surgery for deep infiltrating endometriosis, the risks and benefits must always be weighed up carefully, because even extensive surgery with complete removal of the endometriosis cannot guarantee the desired pain relief which is the aim of surgery.

3.5 Uterine adenomyosis

Core statement:

The diagnosis of adenomyosis is primarily established clinically, by vaginal ultrasound and/or MRI; confirmation is usually provided only by the histological findings based on the hysterectomy specimen.

Recommendations:

a. Given completion of family planning and presence of respective symptoms, hysterectomy can be recommended.
b. If the patients opts for preservation of the uterus, therapeutic amenorrhea may be induced or a progestin-releasing IUD inserted.

3.5.1 Symptoms

Adenomyosis is defined as the infiltration of the myometrium by endometriosis. The main symptoms are painful, heavy and acyclic bleeding together with infertility [65].

3.5.2 Diagnosis

In clinically suspected cases, the following investigations have proved effective (**Table 4**):

Table 4 Work-up for adenomyosis.

Measure/ investigation	Finding
Past medical history	Dysmenorrhea (including with neurodystonia), hypermenorrhea
Clinical examination	Occasionally tender, enlarged uterus (bimanual, rectovaginal palpation)
Transvaginal ultrasound	Poorly demarcated heterogeneous areas, cystic intramural changes in some cases, areas of variable echogenicity, irregular halo effect, discrepancy between anterior and posterior wall
MRI	Changes in the zonal anatomy of the uterus, Irregular junctional zones on T1- and T2-weighted images, areas of low signal intensity and subendometrial foci of high signal intensity, anterior-posterior wall asymmetry as a sign of muscle hyperplasia

Transvaginal ultrasound is of greatest significance in day-to-day practice with approx. 65–70% sensitivity and 95–98% specificity [89,123]. MRI, with high sensitivity and specificity for the diagnosis of adenomyosis, is also suitable and useful in individual cases [38,101,104,149].

Although desirable, there is no suitable routine method for the histologic confirmation of adenomyosis. Various groups have worked on biopsy methods, while only positive results are exploitable. It cannot be used to rule out the disease (e.g. [99]).

The definitive diagnosis, therefore, is ultimately based on the hysterectomy specimen in most cases. Adenomyosis can occur in isolation or together with various forms of endometriosis. DIE is often associated with adenomyosis [110].

3.5.3 Treatment

If the patient's family planning is complete, hysterectomy represents the most effective treatment [65]. The decision regarding which method to be used for this (vaginal, abdominal, laparoscopically assisted vaginal, total laparoscopic, laparoscopic supracervical) is left to the discretion of patient and surgeon. Vaginal hysterectomy on its own without simultaneous laparoscopy rules out the possibility of peritoneal implant removal, however, and should therefore be the exception. Laparoscopic supracervical hysterectomy (LASH) appears to be suitable for this indication with careful reference to the S1 Guideline of the German Society for Obstetrics and Gynecology (AWMF no. 015-064) as the cervix is involved only in extremely rare cases [14,166]. Irrespective of this general recommendation of hysterectomy, consideration must still be given to the potentially negative consequences of hysterectomy in women with chronic pelvic pain (AWMF Guideline of the German Society for Psychosomatic Obstetrics and Gynecology, AWMF no. 016-001).

The benefit of uterus-preserving surgical treatment for patients wishing to conceive or desiring organ preservation in focal forms of adenomyosis is not demonstrated by studies. If this is attempted in individual cases (e.g. encouraging results by [142]), an MRI scan or preoperative administration of a GnRH analog may be useful for planning the operation [133,143,149]. The risk of uterine rupture during pregnancy or childbirth, especially if

larger myometrial defects arise, should be taken into account in the subsequent management of the patient [149,201].

The use of interventional radiology procedures for the treatment of adenomyosis, such as embolization [26] and MRI-guided focused ultrasound ablation [63], hitherto, should be limited to studies.

Progestogins, oral contraceptives and progestin-releasing intrauterine systems are used as an alternative to hysterectomy [58]. The therapeutic effect is based on the induction of amenorrhea. Contraceptives (monophasic products) and progestins should be taken continuously [44,195].

4 Endometriosis and Infertility

Core statements:

a. While a causal relationship has not been resolved yet, endometriosis and infertility are frequently associated.
b. For the treatment of women with both endometriosis and infertility, appropriate skills and experience in infertility surgery as well as cooperation with centers for reproductive medicine are required.

Recommendations:

a. In women with endometriosis who wish to conceive, implants should be removed surgically to improve fertility.
b. In cases of recurrence, assisted reproductive technologies are superior to repeat surgical interventions in terms of the pregnancy rate. In repeat operations for ovarian endometriosis, the surgery-related potential reduction in ovarian reserve is to be considered.
c. Postoperative treatment with GnRH analogs has not been effective in improving the spontaneous pregnancy rate in infertility patients and is, therefore, not recommended.
d. Any drug treatment of endometriosis alone does not improve fertility and should not be applied from a reproductive medicine perspective.

4.1 Pathophysiology of infertility associated with endometriosis

Infertility and endometriosis are often associated, although it is not clear whether there is a causal relationship. Mechanical alteration of the adnexa is unequivocally accepted as the cause of infertility. However, whether the endometriosis creates an immunologically "hostile" environment for implantation or whether it leads to impairment of sperm transport, Fallopian tube mobility and oocyte maturation is unclear [102]. Nevertheless, results from egg donation programs indicate that oocyte and early embryonic development may be impaired in women with endometriosis [66].

4.2 Medical and surgical treatment

Medical treatment alone

In the presence of rASRM stage I and II endometriosis, no improvement in fertility was shown in a meta-analysis of 16 randomized and controlled studies following medical treatment (GnRH analogs, progestins) compared with placebo or a wait-and-see approach [92].

Surgical treatment

a) Minimal and mild endometriosis (in accordance with rASRM) Two randomized, controlled studies on the effect of surgical removal (coagulation/excision) of endometriotic lesions in patients with infertility and AFS stage I and II endometriosis have been identified: Marcoux et al. [119] and Parazzini et al. [146]. Marcoux et al. randomized a total of 341 patients (average age: 30.5 years, average duration of infertility: 31 months) intraoperatively. Over a follow-up period of 36 weeks, 30.7% of the patients in the group who underwent excision of the endometriosis (50 out of 179) became pregnant compared with 17.7% (29 out of 169; cumulative incidence ratio 1.7; 95% CI 1.2–2.6) in the group who underwent diagnostic laparoscopy alone. The birth rate was not given. Parazzini et al. [146] intraoperatively randomized 101 patients with ASF stage I and II endometriosis who had experienced infertility for 38 months on average. During the follow-up period of at least one year, 12 patients in the excision group (12 out of 54 = 22.2%) and 13 in the diagnostic laparoscopy group (13 out of 47 = 27.6%) became pregnant. No statistically significant difference was found between the results, including in terms of birth rate of n = 10 in each group. In a meta-analysis based on these two studies, Jacobson et al. [94] came up with a positive overall result with respect to a benefit of excision in terms of an improved pregnancy rate, although the magnitude of the effect was uncertain (odds ratio 1.66; 95% CI 1.09–2.51). The confidence interval shows the possible variability in the actual effect in the presence of non-parallel results for the two studies.

In a retrospective cohort study (n = 661) of patients with AFS stage I and II endometriosis undergoing IVF, a 10.7% increase in the first IVF cycle pregnancy rate (29.4% compared with 40.1%, p = 0.004) and a 6.9% increase in the birth rate (p = 0.04; [140]) was found in those patients (n = 399) whose endometriotic lesions were excised before IVF.

b) Deep infiltrating endometriosis No controlled, randomized studies are available for deep infiltrating endometriosis including bowel involvement in which the primary objective was to compare surgical against non-surgical treatment in terms of the pregnancy and birth rates. Some non-randomized studies show that excision of DIE may improve the spontaneous and IVF-induced pregnancy rate [23,39,46,69,98,115,179].

In deep infiltrating endometriosis with bowel involvement, a prospective cohort study showed a significantly higher IVF-induced pregnancy rate when complete surgical removal was performed before [23]. Another prospective cohort study showed a higher pregnancy rate in patients with bowel endometriosis who underwent segmental rectosigmoid resection compared to leaving the bowel endometriosis in place (28.3% compared with 20% p-value not specified; [179]). In another study in pregnant women with DIE who wished to conceive, spontaneous pregnancies were observed only after laparoscopy compared with open surgery [46]. The outcome of a case-control study, on the other hand, indicated that radical, retroperitoneal excision of DIE did not confer any additional benefit in terms of reproductive function (and was associated with a significantly higher complication rate) compared with removal of intraperitoneal lesions alone [55].

In patients with endometriotic cysts, endometrioma excision is superior to fenestration and coagulation in terms of the spontaneous pregnancy rate [7,76]. Preoperative medical treatment does not improve the outcome [53,76].

Postsurgical medical treatment

Postsurgical treatment with GnRH analogs did not produce an improvement in the spontaneous pregnancy rate in infertility patients and is, therefore, not recommended [33,92].

4.3 Assisted reproduction

Intrauterine insemination (IUI)

In the presence of minimal and mild endometriosis, IUI leads to an improvement in the pregnancy rate, while some studies have shown a benefit of ovulation induction compared with spontaneous cycles prior to IUI in terms of the pregnancy [48] and live-birth rate [185]. In one study, in contrast to the initial hypothesis, the cumulative endometriosis recurrence rate after 21 months was significantly higher following stimulation for IUI cycles than following controlled ovarian hyperstimulation for IVF [52].

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)

Data from national treatment registries and current retrospective analyses show similar pregnancy rates following IVF in endometriosis patients compared with patients with tubal factor infertility [141]. Thus, conflicting results in a previous review could not be confirmed [16].

The effect of ovarian endometriomas on the outcome of IVF is unclear. Systematic reviews have shown that surgical treatment for endometriomas is not a prerequisite for success of IVF (i.e. with regard to pregnancy rates) [22,184]. On the other hand, it makes needle insertion easier and reduces the risk of infection. Consideration must also be given to the (very rare) possibility of ovarian cancer arising from endometriosis [120,130]. The question of whether doing without surgery in patients who are desperate to conceive in view of the ovarian reserve potentially being compromised by the ablation [43] arises in the presence of bilateral and recurrent endometriomas in particular [34,176]. The individual decision, based on these considerations, not to operate or re-operate (and thus to do without a histologic analysis or complete excision of the endometriosis as is desirable) but with the risk of relevant ovarian disease being overlooked, is a difficult one and should be made only in consultation with the patient, taking into account existing symptoms, safety concerns and differential diagnostic considerations [34]. If loss of ovarian function is imminent, some authors have considered cryopreservation of oocytes following ovarian stimulation or of ovarian tissue as an option for very young women not wishing to conceive at the present time [57].

In cases of recurrence of extensive endometriosis, assisted reproduction is superior to repeat surgical treatment in terms of the pregnancy rate [145]. Considerations regarding whether to operate yet again or to attempt assisted reproductive techniques without intervention should take into account the tubal status, duration of infertility, the patient's age, the extent of the endometriosis and the endometriosis-induced symptoms not associated with infertility, along with the patient's wishes [6]. Although the possibility of endometriosis exacerbation during stimulation for IVF should be considered this has not been demonstrated in controlled studies [20,21]; nevertheless, the cumulative rate of endometriosis recurrence was 7% for IVF cycles after 21 months in one study [52]. As a general rule, the more extensive the endometriosis and the older the patient, the earlier assisted reproduction should be recommended [107]. Nevertheless, younger patients with endometriosis who wish to conceive should also definitely be made aware of this option. According to a systematic Cochrane review, ultra-long GnRH analog therapy after surgical treatment and (3–6 months) prior to IVF/ICSI leads to significantly higher pregnancy rates in rASRM stage III and IV endometriosis [158,163].

Patient information – Infertility and endometriosis

The surgical removal of endometriotic lesions is generally recommended in women who wish to conceive. It has been shown that an improvement in fertility can be achieved with surgery alone if the Fallopian tubes were intact and the sperm analysis normal. The treatment of these patients should be left in expert hands.

If endometriosis recurs (particularly after several operations), in vitro fertilization is a better way to achieve pregnancy than undergoing surgery again.

5 Psychosomatic Aspects

Recommendation:

Psychosomatic aspects in the treatment of patients with endometriosis should be considered and integrated early on.

Even if the evidence suggests that the pain a woman is suffering is caused by the presence of endometriosis, this does not rule out emotional conflict or psychosocial stress as co-factors. Generally speaking, chronic pelvic pain is accompanied by a considerable loss of quality of life and is frequently associated with a somatoform pain disorder (Guideline: Chronic pelvic pain in women, AWMF Registry no. 016-001). A desire to conceive and dysfunctional sick-role behavior (e.g. avoidance of physical activity), which can have an exacerbating effect on pain, leading to a vicious circle, may be additional psychological stress factors in endometriosis.

The integration of psychosomatic approaches to treatment for patients with chronic pelvic pain against a background of endometriosis (as an adjunct to surgical and medical measures) may, on the other hand, improve the patients' quality of life and their handling of the chronic pelvic pain and thus have a positive influence on treatment outcomes [50,173]. The integration of sex counseling into psychological support is also important.

Many authors are now calling for multidisciplinary approaches to treatment when it comes to dealing with chronic pelvic pain [35,116,178,203]. Causes other than endometriosis should also always be considered in the differential diagnosis of chronic pelvic pain [173,174].

In addition, there are some epidemiological studies that suggest an association between endometriosis and other chronic pain conditions such as migraine and chronic irritable bowel syndrome [111,183].

6 Complementary and Integrative Approaches to Treatment

Core statement:

Owing to the lack of controlled, randomized studies to date on complementary and integrative approaches to the treatment of endometriosis, no recommendations can be made.

Women with chronic recurrent endometriosis and corresponding symptoms may obtain relief of symptoms and an improve-

ment in quality of life from the use of complementary therapies [208]. In particular, these include the methods of acupuncture and Chinese medicine, classical homeopathy, herbal medicine, physiotherapy, etc. This should always be preceded by appropriate clinical screening for potential organ changes (endometriomas, hydronephrosis).
Although results from larger scale, randomized and controlled studies are not yet available, initial investigations clearly point to acupuncture [209] and Chinese herbal medicine having an effect on endometriosis-induced pain [60].

7 Rehabilitation, Follow-up and Self-help

Core statement:
After extensive surgical interventions (particularly for deep infiltrating endometriosis), repeat surgery for endometriosis, or in patients with chronic pain, there is often a need for rehabilitation.

Recommendation:
This need should be assessed and rehabilitation measures or follow-up treatment initiated.

All efforts in the area of rehabilitation are focused on the restoration of physical, mental and social well-being. Coping with a disease that frequently follows a chronic course and is sometimes associated with unavoidable limitations and pain is also an important aspect, however. In Germany, specialist centers exist that have considerable experience in the rehabilitation of endometriosis patients.
Follow-up should be based on symptoms, with the focus being on the patient's quality of life. All doctors should be aware of the limitations of the treatment options – particularly in cases where the endometriosis keeps recurring.
Self-help options exist to assist women with endometriosis in coping with the physical and mental problems they face. The independent endometriosis associations in Germany and Austria, the members of which are sufferers themselves, represent the interests of women with endometriosis. Besides free advice, they can provide addresses of self-help groups, rehabilitation centers and specialist doctors.

Patient information – Rehabilitation and aftercare
Following extensive surgery for endometriosis, additional follow-on treatment is also helpful.
The medical treatment of endometriosis has its limitations. Even after careful surgery in the hands of an expert, many patients continue to suffer from chronic pain – even if all the endometriosis was removed successfully. And not all women wishing to conceive will manage to become pregnant.
In order to cope with the physical and mental problems that women with endometriosis can face, patients should be informed about the opportunities for self-help. The independent endometriosis associations in Germany and Austria, the members of which are sufferers themselves, represent the interests of women with endometriosis. Besides free advice, they can provide addresses of self-help groups, rehabilitation centers and specialist doctors in the different regions.

8 Summary

Endometriosis is one of the most common gynecological diseases. Women affected may suffer a considerable loss of quality of life [96]. Besides the individual health problem, the economic impact caused by the high level of morbidity, reduced work productivity and repeated therapeutic interventions should also be considered.
The etiology and pathogenesis are unclear. There is no known causal therapy. Laparoscopic removal is considered to be the surgical "gold standard". Because the patients affected often wish to conceive and organ preservation is a top priority, radical surgery must often be limited. A patient with asymptomatic endometriosis who does not wish to conceive does not generally need to be treated (exception: hydronephrosis).
Careful patient selection and good interdisciplinary cooperation are prerequisites for surgical therapy in cases of endometriotic infiltration of the bowel, urinary bladder and/or ureter. The extent of surgery must always be weighed up against the morbidity associated with surgery and the unavoidable tendency to recur.
Counseling regarding alternatives to surgery (medical treatment) must be documented as carefully as any decision by the patient not to undergo surgery (despite a clear indication).
While pre-operative medical treatment is not recommended with the products available at present, postoperative administration may prolong the recurrence-free interval in cases of peritoneal endometriosis. Various medical options for the treatment of pain symptoms can be considered as an alternative to the surgical approach or in the event of problems with recurrence, with progestins, monophasic oral contraceptives and GnRH analogs (with concomitant add-back medication to eliminate hypo-estrogenic side effects) having similar efficacy with different adverse effect profiles. Progestin-releasing intrauterine systems are another option.
Hormone therapy alone does not result in an improvement in fertility in endometriosis. Surgical removal of the endometriosis and the associated sequelae increased the spontaneous pregnancy rate in some studies. In the presence of severe endometriosis with destruction of organs (i.e. tubes and ovaries), assisted reproduction may be a better option, although surgery beforehand may increase the associated pregnancy rate. There are other reasons (pain, disease unrelated to pregnancy) for which such surgical correction should be considered in individual cases before planned assisted reproduction.
Almost all patients with endometriosis require medication for pain relief in the course of their disease. Depending on the circumstances, professional pain therapy should be provided, with psychosomatic support where necessary.

9 Important Internet Addresses

http://www.dggg.de
http://www.oeggg.at
http://www.sggg.ch
http://leitlinien.net (http://www.awmf.de)
http://www.AGEndoskopie.de
http://www.endometriose-sef.de
http://www.endometriose-liga.eu
http://www.endometriose-vereinigung.de
http://www.eva-info.at

The validity of the guideline has been approved by the Board of the DGGG [German Society for Gynecology and Obstetrics] and the DGGG Guidelines Commission in August 2013. The guideline will remain valid until September, 2016.

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Note

Oral contraceptives and levonorgestrel-releasing intrauterine systems are not approved for the treatment of endometriosis in Germany. They can, therefore, only be used on an off-label basis.